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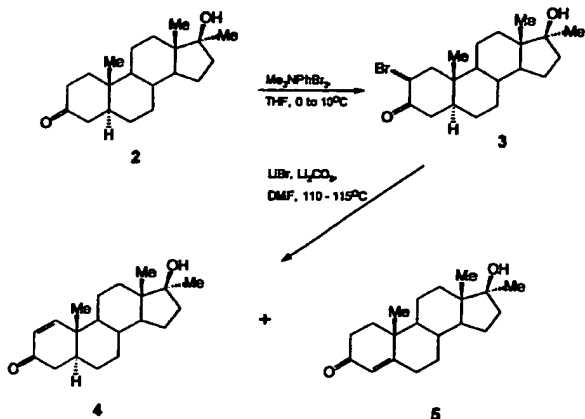
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(54) Title: PROCESS FOR THE SYNTHESIS OF OXANDROLONE



(57) Abstract: A process is disclosed for synthesizing oxandrolone 1 involving the bromination of compound 2 to obtain compound 3, followed by the highly selective de-bromination of compound 3 to obtain compound 4, followed by the oxidation of compound 4 to obtain compound 6, and finally the reduction of compound 6 to obtain oxandrolone 1.

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PROCESS FOR THE SYNTHESIS OF OXANDROLONE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. provisional application serial number 60/290,966 filed May 15, 2001.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] Not applicable.

BACKGROUND OF THE INVENTION

[0003] Oxandrolone (1) is an anabolic steroidal lactone currently being used to promote weight gain and for the relief of bone pain associated with osteoporosis. This invention is directed to a process for making oxandrolone which is efficient and easily scalable.

SUMMARY OF INVENTION

[0004] We have discovered a process by which large quantities of oxandrolone can be produced. We found that the current literature methods to synthesize this compound are not suitable for large-scale production. One aspect of our new scaleable process is shown in Fig. 1.

Bromination of Methylandrostanolone

[0005] One aspect of the present invention provides a process for making a compound of structure 3 comprising providing a compound of structure 2 in a reaction medium selected from the group consisting of an ethereal solvent, a

chlorinated solvent, and acetonitrile; and brominating the compound of structure 2 with a source of electrophilic bromine to obtain the compound of structure 3. By ethereal we mean a liquid characterized by high volatility which often contains an ether. The source of electrophilic bromine may be selected from the group consisting of $R_1R_2R_3R_4NBr_3$, substituted or unsubstituted pyridinium tribromide, N-bromosuccinimide, 1,3-dibromo-5,5-dimethylhydantoin, and molecular bromine, wherein R_1 through R_4 are independently selected from alkyl or aryl groups. By substituted pyridinium tribromide we mean that the ring has substituents which can include alkyl, aryl, halogens, and alkoxy groups. The alkyl group is preferably straight or branched, saturated or unsaturated having from 1 to 6 carbons.

The aryl group may have 1 to 3 rings. The ethereal solvent may be selected from the group consisting of tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane, 2-methoxy ethyl ether, and 1,4-dioxane. The chlorinated solvent may be selected from the group consisting of methylene chloride, chloroform, carbon tetrachloride, and 1,2-dichloroethane. Preferably, the brominating step is conducted at a temperature from -20°C to room temperature and more preferably from 0°C to 10°C . The process can include the further step of recovering the compound of structure 3.

[0006] Bromination of methylandrostanolone 2 (available from Schering-Plough and other suppliers) according to the procedure reported in US patent 3,128,283 (Br_2 , NaOAc, acetic

acid) resulted in an extremely low yield of the desired bromide 3. However, we have discovered that bromination with phenyltrimethylammonium tribromide according to the procedure below gives 3 in 70-90% yield with acceptable purity. Thus, to a THF solution of 2 at 0°C to 10°C is added a THF solution of phenyltrimethylammonium tribromide over 2-3 hours. After stirring for an additional 1-2 hours the reaction is then quenched, preferably with an aqueous solution of sodium carbonate. The layers are then separated, the aqueous layer is extracted, preferably with ethyl acetate, and the combined organic extracts are concentrated to a low volume to give a thick slurry. The product is further precipitated, preferably with n-heptane, cooled, filtered and dried to constant weight to give 2-bromo-17-alpha-methyl-5-alpha-androstan-17-beta-ol-3-one (3) in 70-90%. While THF is the preferred solvent, the reaction can also be run in other ethereal solvents such as diethyl ether, chlorinated solvents such as methylene chloride and chloroform, and acetonitrile. Other nitrogen based tribromides can also be used as a source of electrophilic bromine. For example, under similar reaction conditions pyridinium tribromide gives 3 in 80% yield.

[0007] Bromination with molecular bromine in THF or diethyl ether at ca. 0°C to 10°C also affords 3; however, the purity is somewhat lower compared to bromination with tribromides. Bromination with N-bromosuccinimide as well as with 1,3-

dibromo-5,5-dimethylhydantoin gives 3 but in somewhat lower yield and purity than with tribromides.

Synthesis of Enone 4

[0008] Another aspect of the present invention provides a process of making a compound of structure 4 comprising providing a compound of structure 3 in an aprotic polar organic reaction medium; and debrominating the compound of structure 3 by adding a compound selected from the group consisting of lithium bromide, lithium fluoride, and magnesium bromide along with lithium carbonate to the reaction medium and heating the reaction medium to obtain the compound of structure 4. By aprotic we mean a moiety which neither donates nor accepts protons. The aprotic polar reaction medium may be selected from the group consisting of N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidinone, and N,N'-dimethylpropylene urea. The process can include the further step of recovering the compound of structure 4.

[0009] Treatment of 3 with lithium chloride and lithium carbonate in refluxing DMF according to the US patent 3,128,283 resulted in a low yield of the desired enone 4. In addition, the ratio of 4 to methyl testosterone 5 produced was 3/1 by HPLC analysis of the crude reaction product. We have found that replacement of lithium chloride with lithium bromide according to the procedure below surprisingly gives a

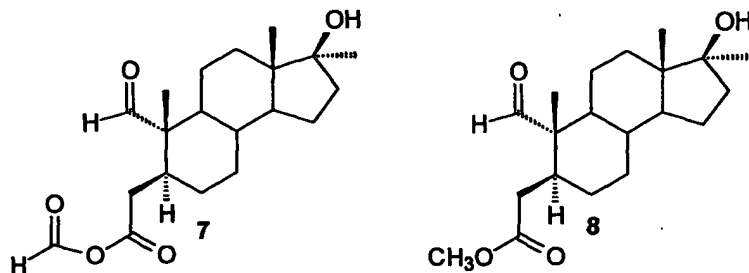
20/1 ratio of 4/5 by HPLC analysis of the crude reaction product. Thus, to a DMF slurry of 3 is added lithium carbonate and lithium bromide. The slurry is then heated at 110°C to 115°C for ca. 2-3 hours. Ethyl acetate is then added at room temperature followed by an aqueous solution of acetic acid. The layers are then separated, the aqueous layer is extracted with ethyl acetate, and the combined organic extracts are washed with water. The organic layer is then concentrated to a low volume to give a thick slurry. The product is further precipitated, preferably with n-heptane, cooled, filtered and dried to constant weight to give 17-beta-hydroxy-17-alpha-methyl-5-alpha-androst-1-ene-3-one (4) in 60-75% from 3. Lithium fluoride or magnesium bromide can be used in place of LiBr but the ratio of 4/5 is lowered to 8/1 and 10/1 respectively. Other polar aprotic solvents such as N,N-dimethylacetamide can also be used.

Oxidation of 4 to 6

[0010] Yet another aspect of the present invention provides a process for making a compound of structure 6 comprising providing a compound of structure 4 in a lower alkanol reaction medium; oxidizing the compound of structure 4 with ozone to form an initial ozonolysis adduct; converting the initial ozonolysis adduct to a salt of the compound of structure 6 by adding a base to the reaction medium; and acidifying the salt to obtain the compound of structure 6. By lower alkanol we mean a straight or branched alcohol having

from 1 to 6 carbons. The lower alkanol reaction medium is preferably methanol. The base can be any alkali metal or alkaline earth metal base but is preferably aqueous sodium hydroxide. The acidifying agent can be any mineral acid but is preferably HCl. The process can include the further step of recovering the compound of structure 6.

[0011] United States patent 3,128,283 describes the oxidation of 4 to 6 using osmium tetroxide in the presence of lead tetraacetate. The extreme toxicity of both of these reagents makes this method clearly undesirable for large-scale production. With this concern in mind, we developed an ozonolysis process for achieving this conversion. US patent 3,109,016 describes the ozonolysis of 4 in carbon tetrachloride to give the formic acid mixed anhydride of 6 (compound 7) after stirring the intermediate ozonide in methylene chloride.



[0012] Alternatively, the methyl ester of 6 (compound 8) is obtained when the ozonolysis is performed in methanol. In both of these procedures, the potentially dangerous ozonide or peroxide intermediates are presumably decomposed thermally.

The use of carcinogenic carbon tetrachloride as the solvent is not suitable for large-scale production. Our method for performing this oxidation calls for ozonation of 4 at -30 to -40°C, preferably in methanol. After the reaction is judged to be complete, the initial ozonolysis adduct is converted to the sodium salt of 6, preferably by the addition of aqueous sodium hydroxide at -10°C. Methanol is then removed and the resulting aqueous solution of the sodium salt of 6, preferably is washed with t-butyl methyl ether. The pH of the aqueous layer is then adjusted to ca. 4, preferably with aqueous HCl, the resulting slurry is then filtered, washed with water preferably followed by n-heptane, and finally dried to give 17-beta-hydroxy-17-alpha-methyl-1-oxo-1,2-seco-A-nor-5-alpha-androstan-2-oic acid 6 in 75-85% yield. The crude product is then recrystallized, preferably from methanol and water, to give recrystallized 6 in 85-95% yield.

Synthesis of Oxandrolone from 6

[0013] The aldehyde 6 was reduced to the seco-acid of oxandrolone via the addition of NaBH₄ to an ethanol/water solution of the sodium salt of 6 at 0-5°C. Upon reaction completion, the pH of the reaction mixture is carefully adjusted to 1-2, preferably with hydrochloric acid. The slurry is stirred for ca. 3 hours at 0-10°C to effect cyclization of the intermediate seco-acid. The slurry of

crude oxandrolone is then filtered, washed, and dried to give oxandrolone (1) in 85-95% yield.

[0014] A still further aspect of the present invention provides a process for making a compound of structure 1 comprising providing a compound of structure 2 in a reaction medium selected from the group consisting of an ethereal solvent, a chlorinated solvent, and acetonitrile; brominating the compound of structure 2 with a source of electrophilic bromine to obtain a compound of structure 3; providing the compound of structure 3 in an aprotic polar organic reaction medium; debrominating the compound of structure 3 by adding a compound selected from the group consisting of lithium bromide, lithium fluoride, magnesium bromide, and lithium perchlorate along with lithium carbonate to the reaction medium and heating the reaction medium to obtain a compound of structure 4; providing the compound of structure 4 in a lower alkanol reaction medium; oxidizing the compound of structure 4 with ozone to form an initial ozonolysis adduct; converting the initial oxonolysis adduct to a salt of a compound of structure 6 by adding a base to the reaction medium; acidifying the salt to obtain the compound of structure 6; providing the compound of structure 6 in an aqueous alcohol reaction medium; reducing the compound of structure 6 to the seco-acid of oxandrolone; and stirring the reaction medium of the seco-acid of oxandrolone to cyclize the seco-acid to obtain the compound of structure 1.

BRIEF DESCRIPTION OF THE DRAWING

[0015] Fig. 1 is a schematic depicting the process according to one aspect of the invention ($\text{Me}=\text{CH}_3$).

DETAILED DESCRIPTION OF THE INVENTION

Example 1: Preparation of 2-Bromo-17-alpha-methyl-5-alpha-androstan-17-beta-ol-3-one (3) using Phenyltrimethylammonium Tribromide

[0016] To a nitrogen purged 50-L 4 neck round bottom flask equipped with an addition funnel, temperature probe, nitrogen inlet adapter, and stirrer apparatus, was added 650 g (2.14 mol) of methylandrostanolone (2) and 5.8 L of THF. The solution was cooled to an internal temperature of 0°C to 10°C . To the solution was added a THF solution of phenyltrimethylammonium tribromide (884 g, 2.36 mol, 2-L of THF) over ca. 1 hour while maintaining an internal temperature of 0°C to 10°C . When the addition was complete the resulting thick slurry was stirred for ca. 1 hour at 0°C to 10°C at which point TLC analysis indicated reaction completion. To the slurry was added an aqueous solution of Na_2CO_3 (377 g in 3.9 L of water) over ca. 1 hour at 0°C to 10°C . Four liters of additional water were added and the mixture was allowed to warm to room temperature. The layers were then allowed to settle for ca. 1 hour and then separated. The aqueous layer was extracted twice with 4 L of ethyl acetate and the combined organic extracts were washed with 4.5 L of water. The organic

layer was then concentrated using vacuum to a volume of ca. 2 L. To the resulting white slurry at ca. room temperature was added 4.6 L of n-heptane over 2 hours. The slurry was cooled to ca. 0°C to 10°C and held at this temperature for ca. 2 hours. The slurry was then filtered through a coarse porosity fritted funnel, washed three times with 600 mL of 0°C to 10°C n-heptane, and dried to a constant weight under high vacuum at ca. 40°C to give 621 g (76% yield) of 2-bromo-17-alpha-methyl-5-alpha-androstan-17-beta-ol-3-one (3) as a pink solid (mp. 195-197°C (uncorrected)).

Example 2: Preparation of 3 using Phenyltrimethylammonium
Tribromide in Methylene Chloride

[0017] To a 0°C to 5°C solution of 2 in CH₂Cl₂ (0.50 g, 1.6 mmol, in 5.0 mL of CH₂Cl₂) was added 0.68 g (1.8 mmol) of phenyltrimethylammonium tribromide in 10 mL of CH₂Cl₂. After stirring for 3 hours at 0°C to 5°C, 2.0 mL of a saturated solution of sodium metabisulfite was added at 0°C to 5°C. Five milliliters of saturated sodium bicarbonate was then added. The layers were allowed to separate, the aqueous layer was extracted with 5 mL of CH₂Cl₂, and the combined organic extracts were washed with 5 mL of water. The organic layer was then dried over Na₂SO₄, concentrated, and dried via high vacuum at room temperature to give 0.57 g of 3 (93% yield) as a tan solid.

Example 3: Preparation of 3 using Phenyltrimethylammonium
Tribromide in Diethyl Ether

[0018] To a 0°C to 10°C slurry of 2 in diethyl ether (0.50 g, 1.6 mmol, 10 mL of diethyl ether) was added a slurry of 0.68 g (1.8 mmol) of phenyltrimethylammonium tribromide in 3 mL of diethyl ether. The reaction was stirred for 3 hours at which point 8 mL of additional diethyl ether was added to improve stirring. The reaction was stirred for an additional 2 hours. Eight milliliters of saturated NaHCO₃ was then added over ca. 5 minutes at 0 to 10°C. Thirty milliliters of additional water was added and the slurry was allowed to warm to room temperature. The layers were then separated and the aqueous layer, which contained some solid material, was extracted twice with 10 mL of ethyl acetate. The combined organic extracts were washed with 20 mL of water, dried over Na₂SO₄, concentrated, and dried via high vacuum to give 0.35 g of 3 (64%) as a tan solid.

Example 4: Preparation of 3 using in Phenyltrimethylammonium
Tribromide in Chloroform

[0019] To a 0°C to 10°C solution of 2 in CHCl₃ (0.50 g, 1.6 mmol, in 5.0 mL of CHCl₃) was added a slurry of 0.68 g (1.8 mmol) of phenyltrimethylammonium tribromide in 10 mL of CHCl₃

After stirring for 1 hour at 0°C to 10°C, 3.0 mL of a saturated solution of sodium bicarbonate was added at 0°C to 5°C. The layers were allowed to separate, the aqueous layer

was extracted twice with 7 mL of CHCl_3 , and the combined organic extracts were washed with 10 mL of water. The organic layer was then dried over Na_2SO_4 , concentrated, and dried via high vacuum at room temperature to give 0.23 g of **3** (36% yield) as a tan solid.

Example 5: Preparation of **3** using Pyridinium Tribromide

[0020] To a 0°C to 5°C solution of **2** in THF (0.50 g, 1.6 mmol, in 5.0 mL of THF) was added 0.51 g (1.6 mmol) of pyridinium tribromide in 4.0 mL of THF. After stirring for 3 hours at 0°C to 10°C , 2.0 mL of a saturated solution of sodium metabisulfite was added at 0°C to 10°C . Five milliliters of saturated sodium bicarbonate was then added. The reaction mixture was then allowed to warm to room temperature. Twenty-five milliliters of ethyl acetate and 25 mL of water were then added and the biphasic slurry was filtered through celite. The celite was washed thoroughly with ethyl acetate. The filtrate layers are separated and the aqueous phase was extracted with 20 mL of ethyl acetate. The combined organic extracts were dried over Na_2SO_4 , concentrated, and finally dried on a high vacuum at room temperature to give 0.49 g of **3** (80% yield) as a white solid.

Example 6: Preparation of **3** using Bromine in THF

[0021] To a 6°C suspension of **2** in THF (0.50 g, 1.6 mmol, in 5.0 mL of THF) was added 88 microliters of bromine in 2.0 mL of THF over 5 minutes. After 1.5 hours of stirring at 0°C to

10°C, 3.0 mL of saturated NaHCO₃ was added to the white slurry.

Five milliliters of ethyl acetate and 2.0 mL of water were then added to the quenched reaction. The layers were then separated and the aqueous layer was extracted with 5.0 mL of ethyl acetate. The combined organic layers were washed with 5.0 mL of water, dried over Na₂SO₄ and concentrated to a solid. The solid was then dried on a high vacuum at room temperature to give 0.57 g of **3** (93%).

Example 7: Preparation of 17-beta-hydroxy-17-alpha-methyl-5-alpha-androst-1-ene-3-one (**4**) using LiBr, Li₂CO₃

[0022] To a 5-liter four neck round bottom flask equipped with a thermoprobe, nitrogen inlet adapter, and mechanical stirrer was added 200 g (0.52 mol) of **3**, and 1.2 L of DMF. To the slurry at room temperature was added 42.6 g (0.58 mol) of Li₂CO₃ followed by 76.2 g (0.89 mol) of LiBr. There was an approximate 10°C exotherm upon addition of LiBr. The slurry was then heated to 110°C to 115°C and held at this temperature for 3 hours at which point TLC analysis indicated reaction completion. The slurry was cooled to an internal temperature of 35°C and 1.4 L of ethyl acetate was added. An aqueous solution of acetic acid (62 mL acetic acid in 600 mL of water) was then added over ca. 0.5 hours. The reaction mixture was then stirred at room temperature for ca. 8 hours and then held at 0°C to 10°C for 2 days. The reaction mixture was then warmed to room temperature, the layers were separated, and the aqueous layer was extracted three times with 1.2 L of ethyl .

acetate. The combined organic extracts were washed three times with 1.0 L of water to remove the majority of the DMF and concentrated via vacuum to a total volume of ca. 500 mL. To the resulting slurry was added 1.8 L of n-heptane over 0.5 hours at room temperature. The slurry was cooled to an internal temperature of 0°C to 10°C and held at this temperature for ca. 2 hours. The slurry was then filtered, washed twice with 200 mL of 0°C to 10°C n-heptane, and dried to constant weight via high vacuum at ca. 45°C overnight to give 128 g (81% yield) of 17-beta-hydroxy-17-alpha-methyl-5-alpha-androst-1-ene-3-one (**4**) as an off-white solid (mp. 153°C - 154°C (uncorrected)).

Example 8: Preparation of **4** using LiBr, Li₂CO₃ in N,N-Dimethylacetamide

[0023] To 5.00 g (13.1 mmol) of **3** in 38 mL of N,N-dimethylacetamide was added 1.95 g (22.4 mmol) of LiBr and 1.06 g (14.4 mmol) of Li₂CO₃. The slurry was then heated at 84°C to 105°C for 6 hours. The slurry was cooled to 8°C and the pH was adjusted to 4 with acetic acid. Thirty-eight milliliters of water was then added dropwise. The resulting slurry was stirred at 0°C to 5°C for 1 hour, filtered, washed with 34 mL of water, and dried via high vacuum at 50°C to give 3.89 g of **4** (97%).

Example 9: Preparation of **4** using LiF, Li₂CO₃

[0024] Five grams (13 mmol) of 3 in 41 mL of DMF was treated with 0.41 g (16 mmol) of LiF and 1.06 g (14.4 mmol) of Li_2CO_3 . The resulting slurry was then heated at 90°C to 93°C for 3 hours. An additional 0.17 g (6.6 mmol) of LiF was then added and the reaction was heated for an additional 6.5 hours at 90°C to 95°C. The slurry was then cooled to 0°C to 5°C. One milliliter of acetic acid was then added followed by 35 mL of water. The slurry was stirred for 45 minutes, filtered, washed with 15 mL of water, and dried via high vacuum at room temperature to give 3.8 g of 4 (96% recovery, 4/5 = 8/1 by area percent HPLC).

Example 10: Preparation of 4 using MgBr_2 , Li_2CO_3

[0025] To 5.00 g (13.1 mmol) of 3 in 40 mL of DMF was added 1.06 g (14.4 mmol) of Li_2CO_3 and 7.26 g (39.5 mmol) of MgBr_2 . The slurry was heated at 100°C to 110°C for 7 hours. The slurry was cooled to 0°C to 5°C. Thirty-five milliliters of 1M HCl was then added dropwise. The slurry was stirred at 0°C to 5°C for 1 hour, filtered, washed thoroughly with water, and dried on a high vacuum at 40°C to give 3.59 g of 4 (91%, 4/5 = 10/1 by area percent HPLC).

Example 11: Preparation of 17-beta-hydroxy-17-alpha-methyl-1-oxo-1,2-seco-A-nor-5-alpha-androstan-2-oic acid (6)

[0026] Two hundred fifty grams (0.828 moles) of 4 was dissolved in 2.5 L of MeOH and cooled to -30°C to -40°C.

Ozone was then bubbled into the solution through a sparge tube. After 6 hours the reaction was judged to be complete by TLC analysis. The solution was allowed to warm to -10°C and an aqueous solution of NaOH (109 mL concentrated NaOH in 3.13 L H_2O) was added dropwise over 2 hours, with an exotherm of 8°C . Once at room temperature, the mixture was concentrated under reduced pressure, with a total of approximately 2.8 L of MeOH being removed. The aqueous solution of the sodium salt was washed twice with 1 L of t-butyl methyl ether, and acidified with concentrated HCl (120 mL) to a pH of 4. The resulting slurry was stirred for about 1 hour after completion of the acid addition, then filtered, washed twice with 300 mL of H_2O followed by 200 mL of n-heptane. The solid product was then dried under high vacuum to a constant weight at 40°C to 60°C to give 210.9 g of **6** (79% yield).

Example 12: Recrystallization of **6**

[0027] To a 50-L four neck round-bottom flask equipped with a stir assembly, condenser, thermocouple, nitrogen inlet adapter, 2-L addition funnel, and heating mantle, were charged 2.96 kg of **6**. To the solids were added 20.7 L of methanol. The solution of **6** was heated to an internal temperature of 59°C . To the solution was added 25.7 L of water over a 2 hour period at 59°C to 65°C . When the water addition was complete the resulting slurry was cooled slowly to room temperature by leaving the flask in the heating mantle. The slurry was then

further cooled to 0°C to 10°C and held at this temperature for ca. 2 hours. The slurry was filtered, washed with 1 L of 0°C to 5°C 2/1 water/methanol (by volume), followed by portion-wise washing of the cake with an additional 6 L of the cold 2/1 mixture. The highly crystalline white solid was then dried at 45°C in a high vacuum to constant weight to give 2.11 kg (71% yield) of recrystallized 6 (mp = 176°C - 179°C (uncorrected)).

Example 13: Preparation of Oxandrolone (1,17-beta-hydroxy-17-alpha-methyl-2-oxa-5-alpha-androstane-3-one)

[0028] Two hundred six grams (0.64 moles) of 6 was slurried in 1.54 L of ethanol and 1.54 L H₂O. The slurry was cooled to 0-10°C using ice water. Sodium hydroxide (74 mL of a 9.5 M aqueous solution, 0.70 moles) was added dropwise over ten minutes. To the resulting solution was added 36.29 g (0.96 moles) of NaBH₄ in portions over 1.5 hours. After stirring for an additional 1 hour after the completion of the addition, the reaction was judged to be complete by TLC analysis. The pH of the solution was carefully adjusted to 1 to 2 by the addition of 6 M aqueous HCl. The resulting slurry was allowed to stir for an additional 3 hours at which point the cyclization reaction was judged to be complete by TLC analysis. The white slurry was then filtered, washed with 250 mL of 0°C to 5°C 1/1 EtOH/H₂O (by volume), 600 mL H₂O, and 700

mL of n-heptane. The solids were dried via high vacuum to constant weight at 40-60°C to give 168.69 g of **1** (86% yield).

CLAIMS

We claim:

1. A process for making a compound of structure 3, comprising:

providing a compound of structure 2 in a reaction medium selected from the group consisting of an ethereal solvent, a chlorinated solvent, and acetonitrile; and

brominating the compound of structure 2 with a source of electrophilic bromine to obtain the compound of structure 3.

2. The process of claim 1, wherein the source of electrophilic bromine is selected from the group consisting of $R_1R_2R_3R_4NBr_3$, substituted or unsubstituted pyridinium tribromide, N-bromosuccinimide, 1,3-dibromo-5,5-dimethylhydantoin, and molecular bromine, wherein R_1 through R_4 are independently selected from alkyl or aryl groups.

3. The process of claim 1, wherein the ethereal solvent is selected from the group consisting of tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane, 2-methoxy ethyl ether, and 1,4-dioxane.

4. The process of claim 1, wherein the chlorinated solvent is selected from the group consisting of methylene chloride, chloroform, carbon tetrachloride, and 1,2-dichloroethane.

5. The process of claim 1, wherein the brominating step is conducted at a temperature from -20°C to room temperature.

6. The process of claim 5, wherein the temperature is from 0°C to 10°C .

7. The process of claim 1, comprising the further step of recovering the compound of structure 3.

8. A process of making a compound of structure 4, comprising:

providing a compound of structure 3 in an aprotic polar organic reaction medium; and

debrominating the compound of structure 3 by adding a compound selected from the group consisting of lithium bromide, lithium fluoride, and magnesium bromide along with lithium carbonate to the reaction medium and heating the reaction medium to obtain the compound of structure 4.

9. The process of claim 8, wherein the aprotic polar reaction medium is selected from the group consisting of N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidinone, and N,N'-dimethylpropylene urea.

10. The process of claim 8, comprising the further step of recovering the compound of structure 4.

11. A process for making a compound of structure 6, comprising:

providing a compound of structure 4 in a lower alkanol reaction medium;

oxidizing the compound of structure 4 with ozone to form an initial ozonolysis adduct;

converting the initial ozonolysis adduct to a salt of the compound of structure 6 by adding a base to the reaction medium; and

acidifying the salt to obtain the compound of structure 6.

12. The process of claim 11, wherein the lower alkanol reaction medium is methanol.

13. The process of claim 11, wherein the base is aqueous sodium hydroxide.

14. The process of claim 11, wherein the acidifying agent is HCl.

15. The process of claim 11, comprising the further step of recovering the compound of structure 6.

16. A process for making a compound of structure 1, comprising:

providing a compound of structure 2 in a reaction medium selected from the group consisting of an ethereal solvent, a chlorinated solvent, and acetonitrile;

brominating the compound of structure 2 with a source of electrophilic bromine to obtain a compound of structure 3;

providing the compound of structure 3 in an aprotic polar organic reaction medium;

debrominating the compound of structure 3 by adding a compound selected from the group consisting of lithium bromide, lithium fluoride, magnesium bromide, and lithium perchlorate along with lithium carbonate to the reaction medium and heating the reaction medium to obtain a compound of structure 4;

providing the compound of structure 4 in a lower alkanol reaction medium;

oxidizing the compound of structure 4 with ozone to form an initial ozonolysis adduct;

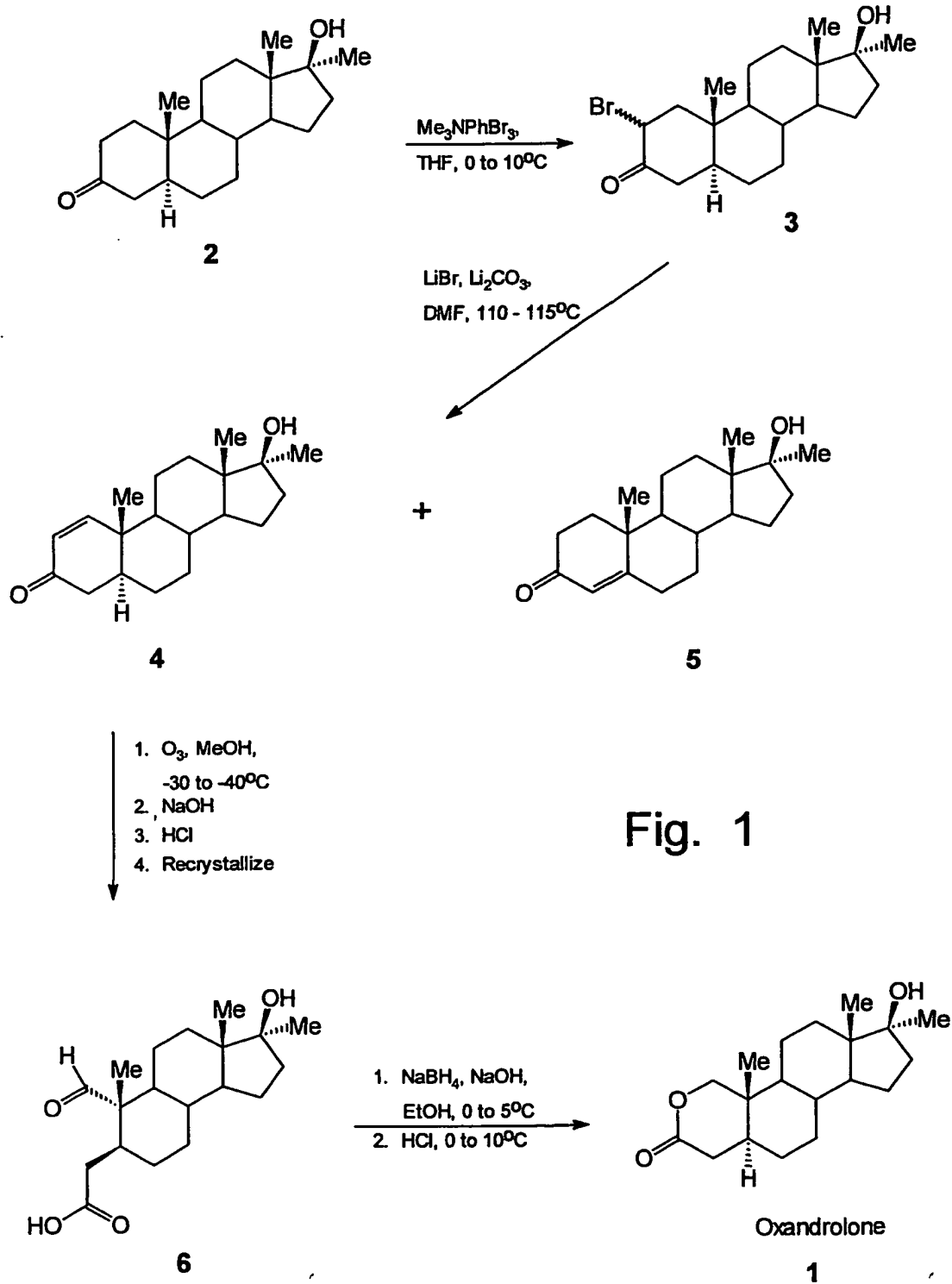
converting the initial oxonolysis adduct to a salt of a compound of structure 6 by adding a base to the reaction medium;

acidifying the salt to obtain the compound of structure 6;

providing the compound of structure 6 in an aqueous alcohol reaction medium;

reducing the compound of structure 6 to the seco-acid of oxandrolone; and

stirring the reaction medium of the seco-acid of oxandrolone to cyclize the seco-acid to obtain the compound of structure 1.



INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/15231

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07J71/00 C07J1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07J C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

BEILSTEIN Data, CHEM ABS Data, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	N. DOORENBOS ET AL: "Synthesis of Some Thiazolosteroids" JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 5, May 1963 (1963-05), pages 414-417, XP002212725 WASHINGTON US	1-6
Y	page 416, column 2, last paragraph -page 417, column 1, paragraph 1	1-16
Y	US 3 128 283 A (R. PAPPO ET AL) 7 April 1964 (1964-04-07) cited in the application examples 2,5	1-16
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

S document member of the same patent family

Date of the actual completion of the international search

6 September 2002

Date of mailing of the international search report

20/09/2002

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/15231

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	RASMUSSEN G H ET AL: "AZASTEROIDS AS INHIBITORS OF RAT PROSTATIC 5ALPHA-REDUCTASE" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 27, no. 12, 1 December 1984 (1984-12-01), pages 1690-1701, XP002043194 ISSN: 0022-2623 page 1700, column 2, last paragraph -page 1701, column 1, paragraph 2	1-16
Y	US 3 101 349 A (RAPHAEL PAPPO ET AL) 20 August 1963 (1963-08-20) column 1, line 33-60; example 2	11-16
X	US 3 280 133 A (RAPHAEL PAPPO ET AL) 18 October 1966 (1966-10-18) examples 1,3	11-15
Y	P. B. SOLLMAN ET AL: "The Absolute Configuration of Sulphoxides: 2-Thia-5.alpha.-androstan-17.beta.-ol Oxides" CHEMICAL COMMUNICATIONS., no. 11, 7 June 1967 (1967-06-07), pages 552-554, XP002212726 ROYAL SOCIETY OF CHEMISTRY., GB ISSN: 1359-7345 page 553, column 1; figure 1	11-15
Y	US 3 281 431 A (SOLLMAN PAUL B) 25 October 1966 (1966-10-25) example 1	11-15
Y	US 3 301 872 A (SOLLMAN PAUL B) 31 January 1967 (1967-01-31) example 7	11-15
Y	H. CHODOUNSKA ET AL: "Synthesis of Some Epitestosterone Analogues" COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS., vol. 59, 1994, pages 435-443, XP002212727 ACADEMIC PRESS, LONDON., GB ISSN: 0010-0765 page 440, paragraphs 2,3	1-10
Y	US 3 109 016 A (RAPHAEL PAPPO ET AL) 29 October 1963 (1963-10-29) cited in the application examples 1-3	11-16

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/15231

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GB 968 206 A (SEARLE & CO) 26 August 1964 (1964-08-26) examples 1,5,10	11-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/15231

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